

Remarks

Claims 43-54 remain in consideration for this application, with claims 43 and 49 being in independent format. Claims 43, 48, 49, and 50 are currently amended. Claims 1-34 have been previously withdrawn and claims 34-42 and 53 are cancelled.

Claims 43-54 were rejected under 35 U.S.C. 112, first paragraph, because it was alleged that the specification did not provide enablement for how to make and use the invention commensurate in scope with the claims. Specifically, it was alleged that the present invention is not enabled for detecting cytogenetic abnormalities in "any" individual. Applicants respectfully assert that since humans, dogs, cats, mice, and whales all have chromosomes, those of skill in the art would be able to screen the individual for a cytogenetic abnormality using the hybridization probes for any of the individuals mentioned. The methods of the present invention require the use of DNA. Deoxyribonucleic acid (DNA) of any type and from any source can be utilized by one of skill in the art in practicing the methods of the present invention. Further, cytogenetic abnormalities can be located in any DNA. Therefore, Applicants assert that because DNA from any source and of any type is the same and that cytogenetic abnormalities can occur in any DNA, The methods described and claimed in the present application could be practiced in any organism having chromosomes.

As a part of the enablement rejection under 35 U.S.C. 112, first paragraph, the Wands factors were cited as factors to be considered in determining whether a disclosure would require undue experimentation. Throughout this entire Wands analysis, Applicants would like to note that the claims are method claims, not product claims. Thus, if the claimed method could be practiced by one of skill in the art under any

conditions using DNA from any source, the claims are enabled. Applicants respectfully assert that the present invention does not require undue experimentation and that those of skill in the art would have possession of the present invention from the disclosure of the Application. In response to the analysis of the Wands factors, Applicants assert:

The nature of the invention and breadth of the claims

In support of the allegation that the methods of the present invention require undue experimentation, it was alleged that the claims of the present invention are drawn broadly to a method of screening “any” individual, which could encompass cats, dogs, whale, etc. Applicants respectfully assert that the methods of the present invention require DNA in order to screen the DNA for a cytogenetic abnormality using the methods of the present invention. Therefore, those of skill in the art could screen “any” individual for a cytogenetic abnormality using the methods of the present invention, as long as the individual has DNA.

Also in support of the allegation that the methods of the present invention require undue experimentation, it was alleged that the claims are broadly drawn to encompass deletions, insertions, translocations, duplications, etc. Applicants respectfully assert that the methods of the present invention would not require undue experimentation for one of ordinary skill in the art to locate “any” cytogenetic abnormality. The method of the present invention uses hybridization probes to detect chromosomal rearrangements occurring within 600 kb of the terminal nucleotide of the chromosome (Example 1, page 51). These chromosomal rearrangements encompass insertions, deletions, translocations, duplications, substitutions, etc. A representative number of probes detecting these types of chromosomal rearrangements are disclosed in the application. There are 56 examples

of probes which hybridize to detect a chromosomal rearrangement in the subtelomeric region of the chromosome. Countless others could have been found using the methods of the present invention exactly as described in the application as the steps of the method do not change. Furthermore, for method claims to be patentable, it is the steps that must be described. Certainly 56 examples demonstrating applicability of the method in various types of cytogenetic abnormalities is strong evidence of enablement since the method steps will not change based on the source of DNA used. Applicants assert that using the methods of the present invention and the disclosed examples of probes, those of skill in the art would have the benefit of the present invention and, thus, would be able to detect a cytogenetic abnormality in any individual having DNA, as long as a cytogenetic abnormality was present.

The amount of direction or guidance

In support of the allegation that the methods of the present invention require undue experimentation, several excerpts from the specification were cited. Applicants agree with the statements presented which outline the problems of the methods utilized in the prior art. For example, it is cited that "The specification many probes are known for FISH analysis of chromosomes, although the exact sequences and location have not been accurately determined [*sic*]." This statement is inferred from page 6, lines 10-14 of the specification, under the heading "Description of the Prior Art", which reads, "Conventional probes suffer from many deficiencies including the fact that they are unsequenced and therefore, their locations have not been accurately determined in chromosomes. By comparison of the sequences of available sequence tagged sites (STS)

contained within these probes, it has been demonstrated that several of these probes contain sequences that are considerable distances from the telomere (millions of base pairs)." It is cited that the specification teaches that in normal individuals there are 2 copies of a sequence and 2 sites of hybridization. Applicants agree with this statement taken from a discussion of the prior art outlining the problems of traditional FISH probes, the problems of which are solved by the methods of the present invention.

It is next cited that, "the specification teaches that many conventional FISH probes contain telomeric DNA and thus are found to hybridize to many internal sequences in chromosomes." Applicants respectfully assert that the section cited for this interpretation comes from page 6, lines 20-25, which is taken from the "Description of the Prior Art" section of the specification outlining problems present in the prior art. This is also the case regarding the next three citations of the specification from page 7 lines 10-20 and page 10, line 25, all taken from the section "Description of the Prior Art."

Applicants assert that all of these statements actually lead one to the conclusion of the patentability of the methods claimed herein as the problems of the prior art are overcome using such methods.

The next citation states, "the specification further teaches that the probes are based on the human genome and become more accurate (predictable) as more data is determined" (p. 14, first paragraph). This paragraph is part of the Summary of Invention and states, "Because the human genome sequence is considered to be more accurate as additional data are incorporated in more recent versions of the sequences, currently designed probes are compared to these versions of the genome sequence to determine if coordinates of designed probes remain within 300 kb of the end of the chromosome."

This section describes the cross-referencing step completed to ensure that the subtelomeric interval used is still appropriate.

Finally, it is alleged that the specification lists a number of probes specific to telomeric regions but does not teach the sequences of the probes and only teaches the sequences of the primers. Applicants respectfully assert that the present invention is drawn to a method of screening an individual for cytogenetic abnormalities and not directed towards the probes themselves. Using the method of the present invention those of skill in the art would be able to determine the sequence of a probe which hybridizes to a particular sequence in the subtelomeric region associated with a cytogenetic abnormality using the methods disclosed herein. Additionally, since the probes utilized in the methods of the present invention are of known sequence and location prior to hybridization, one of skill in the art would be able to determine the sequence of the probe prior to hybridization.

Applicants assert that the amount of direction or guidance in this application is found in the examples covering the process of screening an individual for a cytogenetic abnormality. These examples go into great detail teaching the entire process as disclosed in the present invention. There is a great deal of guidance such that one of skill in the art would be able to screen an individual for a cytogenetic abnormality using the methods of the present invention without undue experimentation. Example 1 teaches the process of developing single copy probes in accordance with the present invention, including probe design, probe generation, labeling, and validation. Also described are how to characterize probes which hybridize to more than one chromosomal region and a section discussing how to ensure that probes are close to the ends of the chromosomes. (see

Example 1, pgs. 25-52). Example 2 describes the design, synthesis, validation, and hybridization of one of the representative number of probes disclosed in the application. This example teaches the method of the present invention using a specific example, which those of skill in the art can use to guide them through the process of the present invention. These Examples together with the summary of invention and 56 examples of probes that were created using the methods of the present invention, one of skill in the art would easily be able to utilize the methods of the present invention to screen an individual for cytogenetic abnormalities without undue experimentation. The specification provides teaching and guidance to practice the methods of the present invention in an amount that is more than sufficient for those of skill in the art.

Presence and Absence of working examples

It was alleged that the specification does not provide any working examples of non-human individuals assayed for cytogenetic abnormalities. Applicants respectfully assert that the working examples show screening for a cytogenetic abnormality using DNA and all individuals mentioned (dog, cat, mice, whale, etc.) have DNA, therefore, the working examples contained in the specification are adequate for those of skill in the art to screen the DNA of an individual for a cytogenetic abnormality.

It was additionally alleged that the specification contains no working examples in which a chromosome imbalance was correlated with a disorder such as idiopathic mental retardation or cancer. Applicants respectfully assert that inherent in the methods of the present invention is the idea that the individuals being screened exhibit a clinical symptom associated with idiopathic mental retardation or cancer which would cause one

of skill in the art to conduct the investigation into whether or not a cytogenetic abnormality exists. Therefore, those of skill in the art would not require an example showing correlation of a condition with a cytogenetic abnormality to practice the invention, as one of skill in the art would have the knowledge needed to carry out such correlation.

Finally, it was alleged that the specification does not provide any working examples in which a representative number of abnormalities are detected. Applicants respectfully assert that the disclosure of 56 examples of probes used to practice the methods of the present invention is sufficient for those of skill in the art to practice the invention. Applicants have asked for guidance as to what number would be a sufficient number of representative examples and did not receive any. Applicants assert that more examples could be provided with a declaration; however, it is Applicants' understanding that there is currently no limit to the amount of representative examples that could be disclosed that would be satisfactory. However, in light of the arguments presented above, Applicants assert that 56 examples is a representative number of examples showing the outcome of using the methods of the present invention. Again, it is noted that the claims are method claims, not product claims and therefore, the question of enablement should be whether or not one of skill in the art would be able to make and use the invention commensurate in scope with the claims. In this respect, Applicants assert that those of skill in the art would be able to use the methods as claimed herein to make and use a multitude of probes. Because DNA is the same in chemical structure across all organisms, the methods are applicable to any organism and there is no reasonable

scientific basis to claim that the claimed methods would need to be changed or modified depending on the organism of interest.

The state of prior art and the predictability or unpredictability of the prior art

It was alleged that Rogan teaches methods of detecting chromosome imbalances and cytogenetic abnormalities in humans and Carter teaches the results of a workshop on detection of cytogenetic abnormalities by probe hybridization. Applicants respectfully assert that there are many differences between the methods of the present invention and those described in Rogan and Carter. Applicants assert that the state of the prior art is summarized sufficiently and accurately in the specification under the heading "Description of the Prior Art" (p. 2-11) and that the specification further teaches those of skill in the art how to overcome the problems of the prior art with respect to predictability or unpredictability.

The level of skill in the art

Applicants agree with the assessment that skill level in the art is high. Furthermore, Applicants note that such a finding weighs in favor of a determination of enablement.

Quantification of experimentation necessary

It was alleged that in order to practice the invention as claimed one would first have to establish probes and methods that would result in a predictable hybridization that would allow detection in any individual. Applicants respectfully assert that this step is also taught in the present application. Those of skill in the art would be able to take the

methods described herein and apply those methods to any probe that they knew of or later identified. To not grant protection to Applicants on this basis is not protecting what Applicants truly invented, namely a method of finding genetic abnormalities. There are 12 reference probes disclosed which illustrate that the probes of the present invention hybridize to the correct chromosome. These test probes would not have to be reproduced in order to practice the methods of the present invention. There would not be any “trial and error experimentation” as was alleged. Additionally, it was alleged that the specification and art teaches that probes do not predictably detect cytogenetic abnormalities and therefore it would be unpredictable to associate the hybridization of a probe with a cytogenetic abnormality. Applicants respectfully assert that this information was taken from the section of the specification describing methods used in the prior art. As stated earlier when this inference, taken from the “Description of the Prior Art” section was cited, the unpredictability described is characteristic of the probes of the prior art, the problems of which are overcome by the methods of the present invention.

It was alleged again that the methods of the present invention could not be used to detect any cytogenetic abnormality in any individual. Applicants respectfully assert that the methods of the present invention provide adequate teaching and examples which would allow one of skill in the art to practice the present invention for any individual with a cytogenetic abnormality in the individual’s DNA. Supporting arguments are discussed above and Applicants direct attention to these comments as they are also applicable here.

Next, it was alleged that the present invention does not teach one of ordinary skill in the art to make probes that will predictably hybridize to a single genomic location

resulting in a single hybridization signal. Specifically it was alleged that “Alternatively, one could have a single signal if one of the two alleles were deleted, but in any genome that has both alleles would not be covered by the claims. Alternatively the claims could be to just probes of the X or Y chromosomes in humans and used to diagnose only men. Since women have two Y chromosomes [*sic*].” Applicants respectfully assert that the methods of the present invention utilize probes that are single copy, therefore, there is only one hybridization signal. The specification on page 24, lines 7-9 states, “Preferably, the probes are single copy probes meaning that they are either represented at a single genomic location or where paralogous sequences are closely linked so that only a single hybridization signal is detected.” Applicants assert that it is taught that the use of a single copy probe results in a single hybridization signal detectable even in the event of closely linked paralogous sequences.

It was additionally alleged that the skilled artisan “would further have to determine which probes and banding patterns would be indicative of clinical abnormalities in any individuals [*sic*]. This would be replete with unpredictable trial and error experimentation. . .” Applicants respectfully assert that the methods of the present invention are directed towards a method of screening an individual for a cytogenetic abnormality and not diagnosing an individual with a clinical diagnosis. The specification reads on page 23, lines 31-p. 24 line 2, “The method generally comprises the steps of screening the genome of the individual using a plurality of hybridization probes, wherein each of the probes has a length of less than about 25 kb, and detecting hybridization patterns of the probes, wherein the hybridization patterns will indicate cytogenetic abnormalities in the individual’s genome.” Applicants additionally assert that the probes

of the present invention are of known sequence and location, therefore, when a hybridization signal is found, it is known what sequence and where the cytogenetic abnormality has occurred. This would allow one of skill in the art to easily associate the sequence and location with a particular chromosome. There are a various number of clinical symptoms associated with cytogenetic abnormalities found in particular chromosomes and those of skill in the art would be able to easily obtain this information.

In conclusion, Applicants respectfully assert that the methods of the present invention, after analysis of the Wands factors, do not require undue experimentation. From a proper reading of the specification and the examples provided, one of skill in the art would have possession of the present invention without undue experimentation. Accordingly, Applicants assert that this rejection has been overcome.

Claims 43-54 were rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. Applicants respectfully assert that the concerns expressed in this rejection regarding "any" individual and "any" probe have been addressed in the discussion of the 112 rejection above and attention is courteously directed to this section.

It was alleged that the invention encompasses an enormous number of nucleotide molecules. Applicants respectfully assert that those of skill in the art would be able to determine the single copy sequences utilized in the methods of the present invention and would not be considered "enormous" to those of skill in the art. Applicants additionally assert that the span of 600 kb of the terminal nucleotide is a small portion in comparison to the entire genome. Finally, Applicants note that these claims are for the methods, not the probes. The methods can be used with any probes.

It was alleged that the specification does not teach the sequence of any probes and that a representative number of species have not been disclosed. Applicants respectfully assert that this rejection has been addressed in the previous discussion of rejections under 112 and attention is courteously directed to this section. Again, Applicants asked for guidance as to what number would be a sufficient representative number and received no guidance. Furthermore, Applicants assert that the standard should be based on the written description as it applies to the method, not as it applies to the probes that could be used with the method or the abnormalities that could be found using the claimed methods.

It was alleged that *Vas-Cath v. Mahurkar* states "the specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Applicants assert that this quote was in reference to the specification of the specific patent involved in the case and is not meant to be a bright line rule for all patent application specifications, as the intent of the specification is to serve as a guideline allowing those skilled in the art to recognize what is claimed. MPEP Section 2163.02 states that, "[u]nder *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177,

179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).” Applicants assert that the specification of the present application conveys with “reasonable clarity” to those of skill in the art that he or she was in possession of the invention. This is supported by the two detailed examples teaching one of skill in the art how to practice the claimed invention. Additionally, 56 examples of probes successful in locating a cytogenetic abnormality in an individual are disclosed.

It was alleged that “[t]he skilled artisan cannot envision the detailed chemical structure of the encompasses nucleic acids regardless of the complexity or simplicity of the method of isolation.” Applicants respectfully assert that one of skill in the art would not need to envision the chemical structure of the nucleic acid to practice the methods of the present invention. Those of skill in the art have adequate knowledge regarding nucleic acids and probes of the type utilized in the methods of the present invention to successfully practice the invention. Again, Applicants are claiming the method, not the probes. Applicants can submit a declaration from one of skill in the art to this effect if necessary.

Next, it was again alleged that the nucleic acid sequence is required to practice the methods of the present invention. Applicants assert that this rejection has been addressed in the arguments above and attention is courteously directed to this section. Accordingly, Applicants assert that this rejection has been overcome.

Claims 43-48 were rejected under 35 U.S.C. 112, second paragraph, for being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. It was alleged that it is unclear if the terminal nucleotide is in the gene, chromosome, probe, etc. Applicants respectfully assert that the

specification provides several instances where it is made clear that the terminal nucleotide is referring to the chromosome. For example, on page 12, lines 13-14, "Generally, the method comprising searching a moving window beginning at the terminal nucleotide on a chromosome end. . ." and on page 12, lines 17-18, "Preferably, the single copy interval is within about 8000 kb of the terminal nucleotide of the telomere of the chromosome." However, in the interest of advancing prosecution, claim 43 was amended to even more clearly state that the method is applicable to chromosomes. Accordingly, Applicants respectfully assert that this rejection has been overcome.

It was alleged that claim 48 is indefinite in that, "idiopathic mental retardation, or mental retardation and at least one other clinical abnormality, or mental retardation and cancer diseases and not cytogenetic abnormalities. [*sic*]." Applicants have amended the claims commensurate with the suggested language and therefore, assert that this rejection has been overcome.

It was additionally alleged that claim 50 is indefinite for being drawn to correlating chromosomal imbalances with medical conditions. Specifically it was alleged that ". . . claim 49 does not require the chromosome to come from a subject individual, etc. Thus, claim 50 can be drawn to correlating imbalances in bacterial artificial chromosomes, yeast artificial chromosomes, corn chromosome with mental retardation or cancer." Applicants have amended claim 50 to more clearly define that the individuals must be capable of having the medical condition that the abnormality is correlated with. Additionally, Applicants note that those of skill in the art would understand that some chromosomes would not be capable of contributing to mental retardation. Claims must be given their broadest reasonable interpretation. Interpreting this as trying to cover

correlation with mental retardation in an organism that cannot have mental retardation is not a reasonable interpretation of the claims. Accordingly, Applicants assert that this rejection has been overcome.

Claims 43-54 were rejected under 35 U.S.C. 102(b) for being anticipated by Rogan et. al. Applicants respectfully assert that one difference in the present invention, compared to the cited references, is that the sequence and location of the less than 25kb probes are known prior to hybridization. Any hybridization signal, therefore, has a much more specific location. Advantageously, such a result is more precise and accurate than was possible using the cited prior art. Using methods of the present invention, those skilled in the art would know the precise sequence and location the probe hybridizes to, thus providing a clear result when a hybridization signal is found. In this cited reference, as well as the other references cited in the other rejections, once the starting sequence is nick translated, the resulting probes are of unknown size and sequence. Therefore, the probes in the references are detecting sequences within particular chromosomes, but the precise sequences and location to which the probes hybridize are unknown. Additionally, Applicants have amended the claims to read that the methods utilize probes which hybridize within 600 kb of the terminal nucleotide, thus further distinguishing the methods of the present invention from the cited references. It was alleged that that the terminal nucleotide of a chromosome changes due to aging of the cell, proliferation etc. Applicants respectfully assert that there is always a terminal nucleotide of any chromosome at any given time and the methods of the present invention are directed towards methods utilizing probes which hybridize within 600 kb of the terminal

nucleotide. In view of the arguments above, Applicants respectfully assert that these rejections have been overcome.

Claims 34-40 were rejected under 35 U.S.C. 102(b) as being anticipated by Flint, et. al. It was alleged that Flint teaches hybridization to the 13q arm, however, much like the nick translated probes used in the previous reference, the probe that hybridizes is of unknown sequence and location. Therefore, it is unknown where exactly the probe hybridizes in Flint's study, other than the expanse of the 13q arm. Further, any hybridization signal obtained by probes in the cited references will only be as precise, as to sequence and location, as the starting material prior to nick translation. In other words, if the starting material is 100kb in length, the results cannot be more specific as to location of the hybridization and sequence of the probe than stating that the hybridization occurred within that 100kb region. Using the probes of the present invention, of known sequence and location, it is possible to obtain the precise sequence and location of the cytogenetic abnormality on the chromosome. It was additionally alleged that "Flint thus teaches a single hybridization signal from a plurality of probes to a single chromosome". Applicants note that the precise location of such a signal as well as the precise sequence of the probes providing such a signal are not known. In contrast, Applicant's probes have the ability to obtain a single hybridization signal from a plurality of probes to a known single sequence and known location. Thus, the probes of the present invention obtain a much more specific result. Additionally, Applicants have amended the claims to a method for screening an individual for cytogenetic abnormalities wherein "causing said probes to hybridize to the genome of the individual, said hybridization occurring within 600kb of the terminal nucleotide," thus distinguishing the methods of the present

invention from those in Flint and the other cited references. In view of the arguments above, Applicants respectfully assert that the rejection has been overcome.

Claims 34-40 were rejected under 35 U.S.C. 102(b) as being anticipated by Bentz et. al. Applicants respectfully assert that, as in the two references discussed above, the probes in Bentz are of unknown size and sequence after nick translation. Bentz begins with YAC-probes, which are usually around 215 kb, prior to nick translation. Thus, the specificity of Bentz's probes are limited to the sequence and location spanning the entire length of the 215 kb YAC-probe starting material. In contrast, the probes of the present invention provide specificity as to sequence and location of the individual hybridized probe. The probes in Bentz are therefore limited to detection of hybridization to a particular chromosome or chromosome arm, whereas the probes of the present invention are sequence and location specific within that arm. Using the probes of the present invention, it is possible to gain a more specific understanding of the sequence and location of cytogenetic abnormalities. Additionally, Applicants have amended the claims to a method for screening an individual for cytogenetic abnormalities wherein "causing said probes to hybridize to the genome of the individual, said hybridization occurring within 600kb of the terminal nucleotide," thus distinguishing the methods of the present invention from those in Bentz and in the other cited references. In view of the arguments above, Applicants respectfully assert that the rejection has been overcome.

Finally, claims 43-45, 49, and 51 were rejected for double patenting over claims 1 and 3 of U.S. Patent No. 7,014,997. Applicants wish to address this rejection once the claims of the present application are found to be allowable as it is Applicants position that the claims will not be an obvious variant due to the limitation that the probes

hybridize within 600 kb of the terminal nucleotide. However, if it is determined that a double patenting issue does exist, Applicants will file a terminal disclaimer.

In view of the foregoing, it is respectfully submitted that all rejections have been overcome and that the claims as they now stand are patentable over the art of record and a Notice of Allowance appears to be in order and is courteously solicited. Any additional fee due in connection with this amendment should be charged against Deposit Account No. 50-1662.

Respectfully Submitted,

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